Department of Psychiatry

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Reward, Emotion, Learning and Ketamine Study (RELAKS)

PARTICIPANT INFORMATION SHEET

Ethics Approval Reference: R73654/RE001

We would like to invite you to take part in a research project. This sheet provides some information to help you decide whether to do so. Please take time to read this carefully and discuss it with friends, family or your GP if you wish. If there is anything that you do not understand, or if you would like more information, please ask us. Please take time to consider whether you wish to take part.

What is the purpose of the research?

Ketamine is increasingly being used as a treatment for depression, although we still don't fully understand how it affects mood. Glutamate, which is the chemical system in the brain targeted by ketamine, plays an important role in learning and memory. We are therefore interested in how ketamine could affect people's performance on decision making tasks involving learning and memory.
In particular, we are interested in understanding how ketamine can influence the way people learn from rewards (such as winning money) and negative experiences (such as receiving a mild electric shock or losing money). We are also interested in how ketamine changes activity in areas of the brain that are involved in these processes. We can investigate this by using a a kind of brain scan called functional Magnetic Resonance Imaging (fMRI).

Your participation in this study will involve one phone screening interview and four research visits (3 times to the Warneford Hospital and one time to the John Radcliffe Hospital) over the course of 2-3 weeks. In all, your participation will involve the following:

- An initial phone screening assessing your eligibility for the study
- Health screening (including an interview about your mood history, physical examination and questions about your physical health)
- Blood (x2) and urine tests (x2)
- Intravenous administration of the study drug on one occasion (ketamine or placebo)
- Questionnaires (at multiple points during the study)
- Computer tasks (some completed online and some completed in person)
- One MRI scan
- Pain stimulation (administered during the MRI scan)
- Eye tracking whilst completing a computer task
- Collection of saliva samples

Why have I been invited?

You have been invited to take part in this research because you are healthy, between 18 and 45 years of age, and speak fluent English. We will be recruiting up to 70 participants in this research.

However, you will not be able to take part in the study if you meet any of the following exclusion criteria, so please read the list below carefully. If you are not sure whether you meet the criteria, please feel free to discuss this with one of the research team. You will NOT be able to take part in the study if:

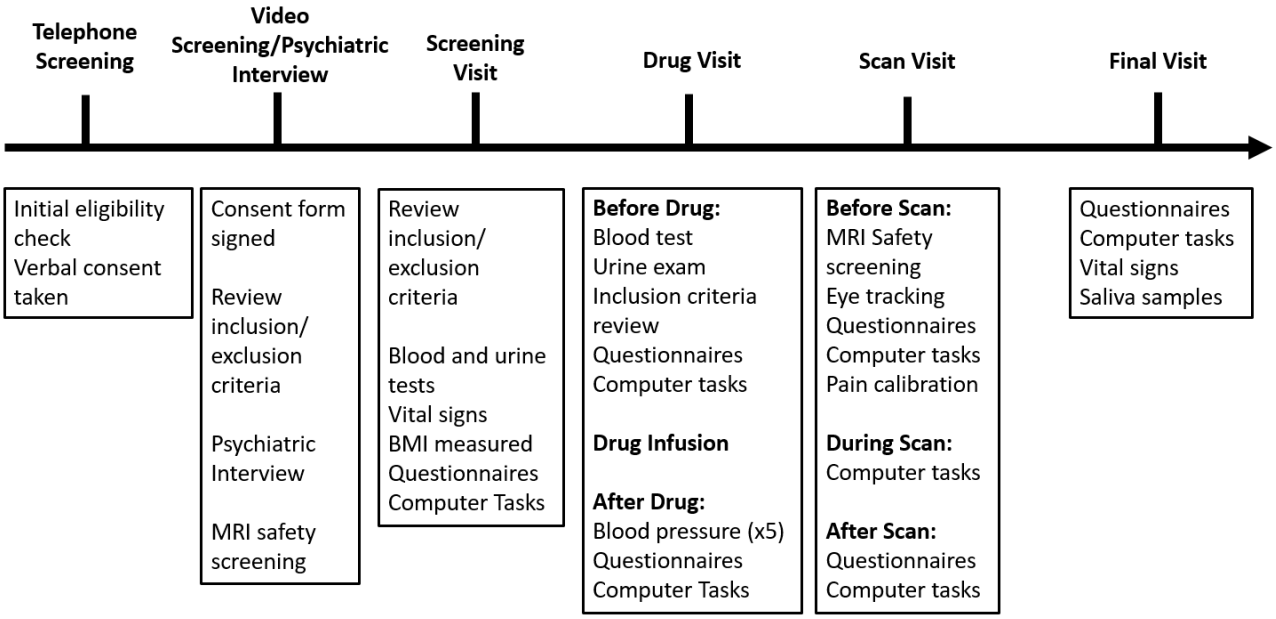
- You have (or have had in the past) any kind of psychological disorder (such as depression, anxiety disorders, bipolar disorder, schizophrenia, or an eating disorder)
- You have (or have had in the past) any medical conditions which may affect your safety in the study or the study results including epilepsy/seizures, brain injury, diabetes, hepatic or renal disease, or severe gastro-intestinal problems (please discuss with the researchers if you think that this may be the case)
- You have a close relative (a parent, sibling, or a child) with a diagnosis of schizophrenia or other psychotic disorder, or bipolar disorder
- You have (or have had in the past) unexplained hallucinations or impulse control problems (e.g. problems with gambling)
- You have (or have had in the past) a heart rhythm disorder
- You have clinically significant high blood pressure (we will test your blood pressure as part of our screening)
- You have increased intraocular pressure/glaucoma
- You are currently pregnant or breastfeeding
- You have abnormal values on the blood or urine tests that we do as part of our screening, which may compromise your safety in the study
- You are currently using any medication that may interact with the study drug or influence performance of the tasks that we ask you to do (the research team will discuss this with you)
- You have taken any recreational drugs in the last 3 months (e.g. marijuana, ecstasy etc.)
- You have ever taken ketamine or phencyclidine at any time in the past
- You regularly drink more than 14 units of alcohol a week (14 units are equivalent to 6 pints of average-strength beer or 10 small glasses of low-strength wine)
- You are not willing to refrain from drinking for 3 days before the infusion visit and 1 day before the final study visits
- You smoke more than 5 cigarettes per day
- You drink more than 6 caffeinated drinks per day
- You have had recurrent rashes or allergic reactions in response to medication in the past
- You have participated in another research study involving the use of medication within the last 3 months
- You have previously participated in a study using the same or similar tasks to those used in this study
- You have any contraindications to MRI scanning (e.g. metal objects in your body, pacemaker, significant claustrophobia, tattoos above the chest)

Do I have to take part?

No. It is up to you to decide if you want to take part in this research. We will describe the research, go through this information sheet with you, and answer any questions you may have. If you agree to take part, we will ask you to sign a consent form and will give you a copy for you to keep. However, you will still be free to withdraw at any time, without needing to give a reason. This would not affect legal rights you would receive. If you are a student at the University of Oxford or Oxford Brookes, there would be absolutely no academic penalty if you decide you do not want to take part, or if you decide to withdraw at any point.

What will happen to me if I take part?

The study will involve four research visits in total, three of these will take place at the Warneford Hopsital and one will take place at the John Radcliffe Hospital (see Figure 1: study timeline). Please be aware that current NHS and government guidance on social distancing and use of PPE will be followed at each visit to protect both participants and researchers from COVID-19 infection/transmission.



Screening and Baseline Assessments

After you express your interest in taking part, a researcher will contact you by telephone to tell you more about the study, answer any questions you might have and, and go through a set of initial screening questions to check if you may be suitable to take part. If you decide to take part, you will be invited for a screening session. Part 1 of this screening session may be conducted by telephone/video call depending on the current Covid-19 guidance. Screening (Part 1) will last approximately 60 minutes. At the start, a researcher will go through the participant information sheet with you. If you are happy with the study details, you will be asked to complete and sign an informed consent form indicating your voluntary participation. If we are conducting this session remotely, will we complete the form for you and will ask you to add your signature when you come to Part 2 of the screening. We will then ask you some detailed questions about your health, any medication you are taking, your mental health, and some questions to make sure that it would be safe for you to go in the MRI scanner.

If after Screening (Part 1) you fulfil our inclusion criteria, you will be invited for an on-site Screening Visit (Part2) at the Clinical Research Facility (CRF) or at the Department of Neuroscience, Warneford Hospital. The screening will last between 30-60 minutes. During this visit, we will ask you to provide blood and urine samples, we will measure your height and weight and take your blood pressure. Your heart function will be assessed using a test called an Electrocardiogram (ECG), which consists of putting stickers on your chest that are able to detect details of your heart beat. Finally, to complete the assessment of your general health, you will also receive a physical exam, that will be performed by trained medical personnel. To complete the ECG and the physical examination, you will be asked to remove your top. Please let the study team know if you would prefer to have a chaperone with you during the duration of these exams. At the end of this visit, we will ask you to complete some questionnaires and computer task. In this task, you will watch different facial emotional expressions on a computer screen and you will have to identify them. After the visit, a study doctor will review the results of the blood tests, ECG, and physical exams and he/she will determine if you are a good fit for the study.

Infusion Visit

The next physical visit will be at least one week later and will take place again at the CRF or at the Department of Neuroscience. Two days before this visit we will ask you to complete an online task. We will provide you with login details to complete this task on our study website. The task takes 30-60 minutes and must be completed on the two consecutive days prior to the infusion visit (e.g. if your visit is Monday then the task must be completed on Saturday and Sunday). The task involves choosing between two abstract shapes in a computer game in which you can win money in line with how well you do the task. Your objective will be to learn how frequently these shapes give you a reward through trial and error in the computer task.

On the morning of the infusion visit, we will ask you to come to the Warneford Hospital. You should not drink alcohol from 3 days prior to this visit and you will be asked to fast overnight before the infusion, refraining from solid food and non-clear liquids for 8 hours prior to the infusion. Before the infusion, you will be asked to complete a computer task, which involves choosing between the shapes you learned about from the previous two days. You will also be asked to complete questionnaires and give a urine and blood sample.

You will then be randomly assigned to receive an infusion of either ketamine (0.5mg/kg) or saline. The infusion will be administered intravenously - a nurse or a doctor will put a needle into a vein on your arm or on the back of your hand and then a pump will gradually infuse a low dose of ketamine over 40 minutes. During the infusion you will be lying on a bed. Medical personnel will be present in the clinic at all times. Before, during and after the infusion we will check how you are feeling and ask you to describe and record any symptoms or side effects you may be experiencing. You will remain on the bed until you are ready to get up, most people feel initially unsteady on their feet. After the infusion you will be asked to wait another 2-3 hours under observation to make sure that you would be safe to leave the premises. During this time we will ask you to complete a battery of questionnaires and computerised tasks. Since ketamine may lead to an increase in blood pressure, we will check your blood pressure every 10 minutes during the infusion and every 15 minutes for the hour following the end of the infusion. Once the qualified personnel is satisfied that you are safe to leave, we will book a taxi to take you home. You will be given contact details of a doctor who will be on-call to contact if you experience any issues.

Ketamine is a psychoactive drug – a drug that affects the central nervous system – may impair judgment, thinking, or motor skills, and therefore you should not operate hazardous machinery or drive a motor vehicle until you are reasonably certain that you are capable of doing so and until at least the next day. You should also refrain from signing any legal documents on the same day of the infusion.

Research Visit 1

The next day, you will be asked to come to the Neurosciences Building within the Warneford Hospital site. You will be asked to complete a computer task, which involves choosing between the shapes you learned about in the online memory study, this time with an eye tracker computer. After this, a member of the research team will book a taxi for you and you will be taken to the Wellcome Centre for Integrative Neuroimaging (WIN – formerly FMRIB) at the John Radcliffe Hospital for an MRI brain scan. This visit will last for up to 4 hours. On arrival, one of our research team will meet you to describe what the scan will involve and answer any questions you may have. There you will also be ask to complete some computer tasks and questionnaires. After this, a radiographer will go through a safety checklist to take part in MRI studies, to check that it is safe for you to go into the scanner.

During the MRI scan you will be asked to lie still on a table inside a 7 Tesla MRI scanner. The scan will last up to 120 minutes. Please let us know beforehand if you wear contact lenses or glasses. You will wear a respiration belt to measure your breathing rate and a finger clip to monitor your blood flow. These are standard instruments used to measure physiological responses whilst in the scanner.
During the scan, we will ask you to complete some computer based tasks. In one of these tasks, you will be shown some images on the screen, some of which will be associated with pain stimuli, so sometimes you will receive electrical pain delivered to the back of your left hand. The painful stimuli will be delivered for a very brief duration (less than 1 second) and by a piece of research equipment that produces a low-level electrical output that can induce a moderate and brief pain sensation. The intensity of this pain sensation will be calibrated before the scanning session based on your personal pain sensitivity threshold to be acceptable to you (see below). We experimentally induce these painful sensations in a safe, controlled and temporary manner. The painful stimulations will follow an ethically approved established protocol and has been used previously in approved studies conducted in the University. The electrical pain delivered will be well within the range of what you report as painful during the calibration session. The electrical pain may lead to a skin reaction (for example, a temporary redness of the skin where the shocks were delivered to) which should clear within 2 hours of the scanning session.

The scanning session will take up to 120 minutes and during the course of the scanning you would receive a maximum of 60 electrical pain stimulations.

To prepare for the task involving electrical pain, we will run a calibration session to establish your pain sensitivity threshold. This will be done before the brain scan. This calibration first requires the placing of an electrode on the back of your left hand using adhesive strips along with a commonly used cream to enhance conductance. The calibration process will involve gradually increasing the magnitude of the electric current in small increments. During calibration, your personal experience of pain will be assessed using a 10 point scale on which a rating of 1 is defined as "minimal pain", whereas 10 refers to "worst possible pain". The study will involve electric pain individually calibrated to your intensity 8 on this scale.

After the scanning session, you will complete another decision-making task which involves making choices between the shapes you learned inside the scanner based on which ones you think are better.

Research Visit 2

One week later you will be asked to attend final visit which will take place at the Neurosciences Building, Warneford Hospital. This visit will last approximately two and a half hours. During this visit you will be asked to complete a number of questionnaires and cognitive tasks. One of these tasks will probe how you perform under challenging situations. During this task we will measure your heart rate, and take saliva samples to allow us to measure levels of cortisol and alpha amaylase.

What is ketamine?

Ketamine is an approved anesthetic, a drug used to produce loss of consciousness before and during surgery. During your participation in this study, you will receive a dose an intravenous infusion of 0.5mg/kg of ketamine (total dose) over 40 minutes. This means the medication will be administered directly into your blood stream via the IV line at a sub-anesthetic dosage that has been studied for the treatment of Major Depressive Disorder (MDD) and other stress-related disorders. A sub-anaesthetic dosage means you will not fall asleep during the treatment.

Are there any risks in taking part in this research?

The behavioural tasks used in this study are very commonly used and considered safe.

Potential side effects and adverse reactions to ketamine administration include high blood pressure, local pain in the injection site, confusion, agitation, anxiety, sleepiness or sedation, headache, nausea, drug hypersensitivity, increased urine output, pupil dilation and dissociation (the feeling that the mind and the body are separate), which should resolve quickly post-infusion (usually within one hour since the end of the infusion). Furthermore, rare side effects (0.1-1% occurrence) involve slower breathing, redness of skin, slow heartbeat, tremors, low blood pressure and vomiting . Previous studies examining the antidepressant effects of ketamine have documented side effects of the drug such as distorted visualization of colors, feeling suspended in space or floating, experiencing out-of-body sensations, and vivid dreaming. Some subjects report the psychic experiences as bizarre or frightening, while others describe them as pleasurable, joyful, or fascinating. When such reactions do occur, they are usually mild and short-lasting.

In order to minimise the risks, all participants will be screened for physical or psychological risk factors before enrolment in the study. In addition, a qualified NHS Consultant Psychiatrist will oversee the delivery and all participants will receive detailed instructions on how to behave before and following treatment (e.g. fasting rules, when to avoid driving, cycling, or operating heavy machinery, not signing any legal document) and what to do if they experience any problems following their participation. All participants will be provided with contact details of a research team member whom they can contact at any time if they have any concerns.

MRI is safe and non-invasive and does not involve any ionising radiation (x-rays). However, because it uses a large magnet to work, MRI scans are not suitable for everybody. Because of this, you will be asked pre-screening safety questions to help determine if you are able to take part. We will not be able to scan you if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry other pieces of metal that have accidentally entered your body.

While there is no evidence to suggest that MRI is harmful to unborn babies, as a precaution, the Department of Health advises against scanning pregnant women unless there is a clinical benefit. We will not be able to include you in this study if you are pregnant or breasfeeding.

If you think you might be claustrophobic, please discuss this in advance with the researcher, or let the radiographer or operator know before your scan.

As some of the scans are noisy, we would give you earplugs to make this quieter for you. It is important that these are fitted correctly as they are designed to protect your hearing.

In preparation for your scan and for your comfort and safety we may ask you to change into pocket less and metal free "pyjama-style" top and trousers, which are available in a range of sizes. You may keep your underwear and socks on but we would ask women to remove underwired bras. If you have a suitable non-wired bra you may wear this instead. Please avoid any fabrics that contain metallic threads or have been silver impregnated (often marketed as anti-microbial/bacterial or anti-odour/stink). Metal jewellery including body piercing must also be removed. Eye shadow and mascara must also be avoided, since some types contain materials that can interact with the magnetic field. If you wish to wear eye makeup to your scan we can provide makeup removal wipes. Lockers are provided to secure your personal belongings and clothing.

Some people scanned in MRI scanners, especially 7 Tesla scanners, may experience a mild dizzy sensation as they are moved into the scanner. This is normal and the sensation starts to go away as soon as you are in the scanner.

You will be introduced carefully to the scanner and are allowed to leave at any stage. Whilst you are in the scanner you will have easy access to a call button should you wish to stop the scan or speak with the radiographer or operator.

It is important to note that we do not carry out scans for diagnostic purposes, only for research. Our scans are not routinely looked at by a doctor and are therefore not a substitute for a doctor's appointment. Occasionally, however, a possible abnormality may be detected. In this case, we would have the scan checked by a doctor. If the doctor felt that the abnormality was medically important, you would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. You would not be informed unless the doctor considers the finding has clear implications for your current or future health. All information about you is kept strictly confidential.

The current study will also involve experimentally induced painful stimuli. These will be delivered by a surface electrode attached to the back of the left hand using adhesive strips. It is possible that these electrical pain stimuli may lead to a skin reaction which should clear within 2 hours of the scanning session.

Compliance with COVID-19 Rules and Regulations

All of our clinical and research staff will be complying with UK government, NHS and University of Oxford regulations to tackle COVID-19. In order to safeguard the health and safety of all parties involved, all the aspects of your participation which can be done remotely (e.g. initial screening and filling in questionnaires etc) will be done online and through videoconferencing. The aspects of your participation which will involve personal contact (e.g. taking a blood sample) will be done by personnel who will wear personal protective equipment (PPE) such as mask, apron and disposable gloves.

During your participation we will also ask you to comply with the COVID-19 regulations. This will include: wearing a facial covering (unless a medical exemption that falls outside of exclusion criteria), completing temperature checks before entering NHS or University sites for in-person visits. If you or any members of your household experience symptoms of COVID-19, such as a high fever, a persistent cough or loss or change to your sense of smell or taste, or tested positive for COVID-19 please immediately contact a member of the research team for contact tracing purposes. We will also ask on the day before each in-person visit whether you or a member of your household are at high risk for COVID.

Are there any benefits from taking part in this research?

No. There will be no direct benefit to you from taking part in this research. It is hoped that the results from this research will help us to identify better measures for future studies in patients with major depression.

Will my time/travel costs be reimbursed?

You will receive £250 for taking part in the study and any additional reasonable travel expenses will also be covered (e.g. train or bus tickets). Your performance in the learning and decision-making games will also affect your final reimbursement amount and potentially you can win an additional £50 based on your performance.

What will happen to any samples I give?

We will conduct urine tests in order to screen for pregnancy and drug use during the study. These tests will be conducted at the CRF or at the Department of Neurosciece. Additionally, blood samples will be collected during your screening visit and will be tested for routine tests at the Clinical Biochemistry and Haematology Laboratories at John Radcliffe Hospital. Upon completion of the tests, your sample will be disposed according to NHS Disposal guideline. The results of your test will be reviewed by a physician. We will also collect samples of your saliva to measure the levels of the hormone cortisol and alpha amaylase. Your saliva samples will be anonymised, spun so that no cells will be left, and stored in the Department of Psychiatry at the Warneford Hospital until cortisol is measured, and will be disposed of within six months of the end of the study.

What will happen to the data provided?

The information you provide during the study is the **research data**. Any research data from which you can be identified is known as **personal data**. For this study, we will ask you to provide your name, date of birth, years of education, medical history, contact number and a residential address and bank account details for study payment.

Personal data will be stored in a locked cabinet in the Neurosciences Building within the Warneford Hospital site and will only be accessible by the study team. Your personal data will be destroyed after 5 years from study completion date and the only information that we will keep will be your research ID number. Once the study is completed a linkage list which ties your personal information to your research data through your unique ID number will also be destroyed.

All de-identified research data (e.g. your responses in the learning tasks, questionnaire responses) will be kept for a minimum duration of 5 years. De-identified MRI scans and other physiological measurements that are retained at the department will be stored in perpetuity. De-identified and fully anonymised research data may be made available at the time of the publication of this study in scientific journals to facilitate data sharing with other researchers.

Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the research.

Will the research be published?

The results of this study may be published in a scientific journal and might also be presented at scientific conferences. In any publication resulting from this study, all data will be anonymised and backtracking to individual participants will not be possible. The University of Oxford is committed to the dissemination of its research for the benefit of society and the economy and, in support of this commitment, has established an online archive of research materials. This archive includes digital copies of student theses successfully submitted as part of a University of Oxford postgraduate degree programme. Holding the archive online gives easy access for researchers to the full text of freely available theses, thereby increasing the likely impact and use of that research. The research will be written up as a student's thesis. On successful submission of the thesis, it will be deposited both in print and online in the University archives to facilitate its use in future research. If so, the thesis will be openly accessible.

Who has reviewed this research?

All research studies are checked by an ethics committee to ensure the research is conducted safely and to the best standards. This research has been reviewed by, and received favourable opinion from, the University of Oxford Central University Research Ethics Committee.

Who is organising and funding the research?

This study is funded by the UK Medical Research Council and the research is being sponsored and organised by the University of Oxford.

Who do I contact if I have a concern about the research or I wish to complain?

If you have a concern about any aspect of this research, please contact Dr Erdem Pulcu, Erdem.Pulcu@psych.ac.uk, or Prof Catherine Harmer, Catherine.Harmer@psych.ac.uk and we will do our best to answer your query. We will acknowledge your concern within 10 working days and give you an indication of how it will be dealt with. If you remain unhappy or wish to make a formal complaint, please contact the Chair of the Medical Sciences Interdivisional Research Ethics Committee (MS IDREC) at the University of Oxford who will seek to resolve the matter as soon as possible - Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD.

Data Protection

The University of Oxford is the data controller with respect to your personal data, and as such will determine how your personal data is used in the research.

The University will process your personal data for the purpose of the research outlined above. Research is a task that we perform in the public interest.

Further information about your rights with respect to your personal data is available from https://compliance.web.ox.ac.uk/individual-rights.

Further Information and Contact Details

If you would like to discuss the research with someone beforehand, or if you have any questions afterwards, please contact Dr Erdem Pulcu, erdem.Pulcu@psych.ac.uk or phone (01865) 613154.